# Draft ICCVAM Recommendations

## Using Fewer Animals to Identify Chemical Eye Hazards: Revised Criteria Necessary to Maintain Equivalent Hazard Classification

### *Background and Rationale*

Current U.S. Federal Hazardous Substance Act (FHSA 2008) regulations provide procedures to determine the eye hazard classification and labeling requirements for chemicals and products to which consumers may be exposed. The current procedure requires a minimum of 6 animals per test and may require up to three sequential tests for each substance, thereby requiring 6, 12, or 18 animals to reach a hazard classification decision. The requirement for second and third sequential tests is based on the number of positive responses in the previous test.

In 2002, the Organisation for Economic Co-operation and Development (OECD) Test Guidelines Program adopted U.S. proposed revisions to Test Guideline 405: Acute Eye Irritation/Corrosion (OECD 2002) that reduce the maximum number of required animals per test from 6 to 3. The Animal Welfare Act (AWA 2010) and the Public Health Service Policy (PHS 2002) similarly require that only the minimum number of animals necessary to obtain scientifically valid results should be used and that a rationale for the appropriateness of the number of animals used be provided to and approved by the Institutional Animal Care and Use Committee. In light of this policy and regulations, most *in vivo* ocular safety testing is expected to adhere to the 3-animal procedure described in OECD Test Guideline 405 (OECD 2002) and in a test guideline issued by the U.S. Environmental Protection Agency (EPA 1998). However, current FHSA regulations do not provide criteria to classify results from a 3-animal test. Therefore, an analysis was conducted to determine classification criteria based on results from a 3-animal test that would provide eye hazard classification equivalent to procedures in current FHSA regulations (Haseman et al. 2011).

In the analysis, the frequency that current FHSA classification criteria identify substances as ocular irritants was compared with the frequency that a classification criterion of either at least one or two positive animals in a 3-animal test would identify these substances. A number of different underlying population positive response rates for identifying

substances as ocular irritants were examined. A NICEATM database of 481 rabbit eye test studies using 6 animals was also used to estimate over- and underprediction rates for each criterion using a mixture of three binomial distributions. In each instance, a classification criterion of at least one positive animal in a 3-animal test more closely matched the expected outcome based on current FHSA regulations, while a criterion of at least two positive animals in a 3-animal test identified far fewer irritants. These results showed that using a classification criterion of at least one positive animal in a 3-animal test to identify eye hazards will provide the same or greater level of eye hazard classification as current FHSA requirements, while using 50% to 83% fewer animals. ICCVAM developed the following draft recommendations based on the results of this analysis.

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ICCVAM concludes that using a classification criterion of at least one positive animal in a 3-animal eye safety test to identify chemicals and products that are eye hazards will maintain the equivalent level of eye hazard classification as current FHSA requirements (16 CFR 1500.42), while using 50% to 83% fewer animals. ICCVAM therefore recommends the use of this classification criterion together with ocular safety testing procedures that use a maximum of 3 animals per test substance. Implementation of this recommendation will harmonize the number of animals used for eye safety testing across U.S. regulatory agencies and international test guidelines.